
Organic reaction mechanisms

Answers to worked examples

WE 19.1 Breaking bonds to form ions or radicals (on p. 867 in *Chemistry*³)

Use curly arrows to show the products formed on (a) heterolysis and (b) homolysis of the C–Br bond in Me₃C–Br.

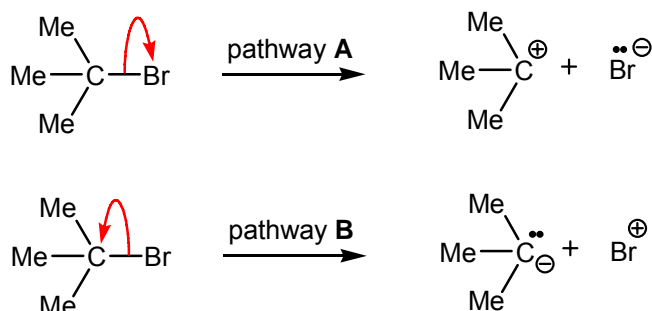
Strategy

Using a “double-headed” arrow symbolises the movement of a pair of electrons. By comparison, a “single-headed” arrow symbolises the movement of a single electron. Heterolytic cleavage of a bond involves unsymmetrical fragmentation to give an anion and a cation, and homolytic cleavage involves symmetrical fragment to give two radicals.

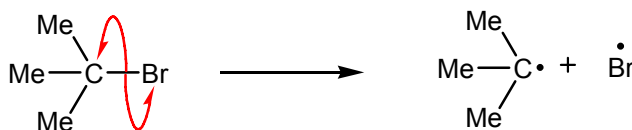
- (a) Unsymmetrical heterolytic cleavage of an unsymmetrical bond, C–Br, has two different pathways. The more favour pathway will lead to the more stable cation and anion.
- (b) Symmetrical homolytic cleavage of an unsymmetrical bond, C–Br, has one pathway.

Solution

- (a) There are two potential pathways, **A** and **B**, for unsymmetrical heterolytic cleavage of this unsymmetrical C–Br bond. Pathway **A** is more favoured as it leads to the formation of a relative stable tertiary carbocation (Me₃C⁺) and a stable bromide (Br[−]) anion. Pathway **B** is disfavoured as it leads to an unstable carbanion and a bromonium ion. The curly arrow starts at the centre of the C–Br bond (where the pair of sigma electrons resides) and the “double-headed” arrow ends at the chosen atom.

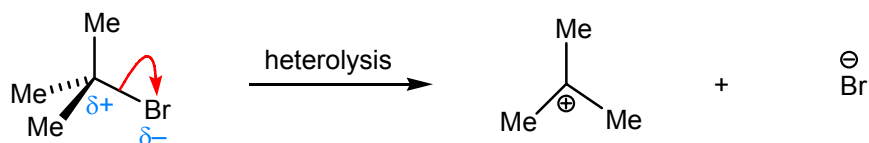


(b) Symmetrical homolytic cleavage of this unsymmetrical C-Br bond leads to two radicals, $\text{Me}_3\text{C}^{\bullet}$ and Br^{\bullet} . There are two “single-headed” curly arrows, which start at the centre of this C-Br bond (one for each electron present in its sigma bond) and each “single-headed” arrow ends at each atom of this bond.

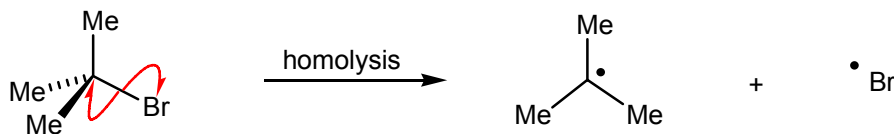


Answer

(a)

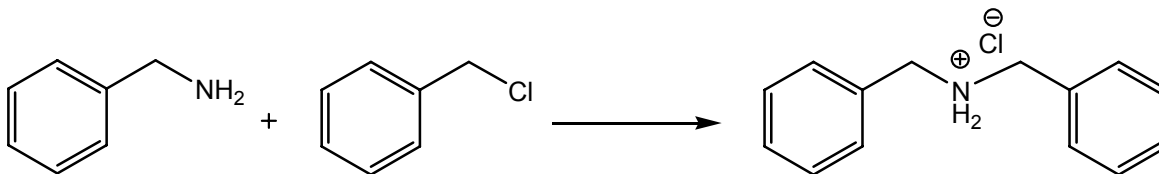


(b)



WE 19.3 Spotting nucleophiles and electrophiles (on p. 881 in *Chemistry*³)

(a) In the following reaction, which reactant is the nucleophile and which is the electrophile?



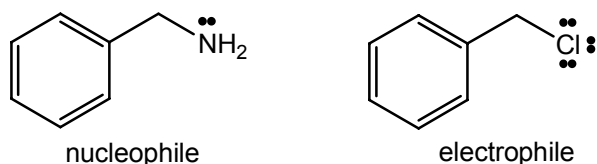
Strategy

A nucleophile is a reagent, which reacts with an electrophile, to form a covalent bond by donating its pair of non-bonding electrons. This nucleophile **MUST** have a pair of electrons to donate, and this electrophile **MUST** have an empty orbital to accept them.

Draw out both reagents and include any non-bonded pairs of electrons.

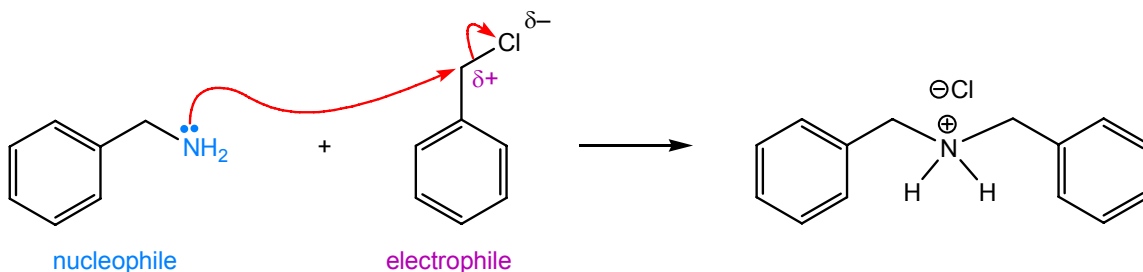
Solution

Benzyl amine is the nucleophile as it forms a covalent C-N bond by donating its pair of non-bonded electrons. Therefore, benzyl chloride is the electrophile in this reaction (even though it does contain three non-bonded pairs of electrons on its chlorine atom).



- (b) Use curly arrows to show the mechanism of the reaction and draw the product that is formed.

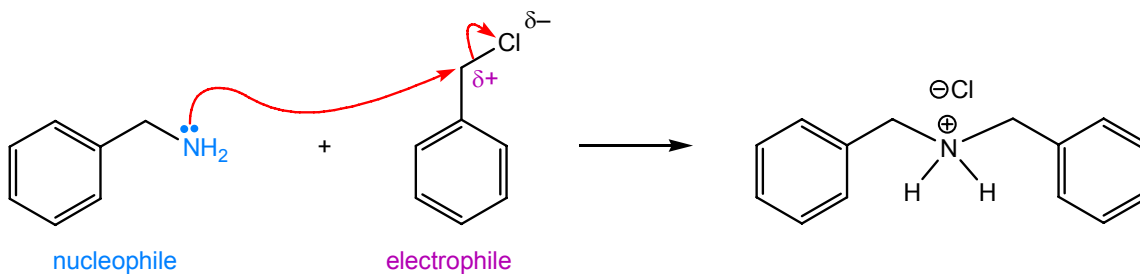
The first curly arrow, a, starts at the non-bonded pair of electrons on the nitrogen atom of the nucleophile, benzyl amine, and ends at the carbon atom of the electrophile, benzyl chloride to form the **blue C-N** bond.



As this curly arrow involves the movement of a pair of electrons it has a “double-headed” arrow. Simultaneously, a second curly arrow, b, is needed to prevent the carbon atom of this electrophile from having 10 valence electrons. This “double-headed” curly arrow symbolises the heterolytic cleavage of the C-Cl bond to give a chloride anion; the curly arrow starts in the centre of this C-Cl bond, where the two sigma electrons resides, and ends on the chlorine atom, to give the chloride, Cl⁻, anion

Answer

(a) and (b)

**WE 19.5 Assigning oxidation levels (on p. 898 in *Chemistry*³)**

Assign oxidation levels to the carbon atoms in **A–C**. Use these values to determine if the transformations of **A** → **B** and **B** → **C** involve oxidation, or reduction, or neither.

Strategy

To answer this question, you will need to work out if the oxidation level of each carbon atom has increased, decreased or stayed the same during these reactions. If the oxidation number increases, then it is an oxidation, if it decreases, then it is a reduction, and if it stays the same, it is neither. If you are unsure how to assign oxidation levels of organic compounds; see Table 19.2 on page 899 in *Chemistry*³.

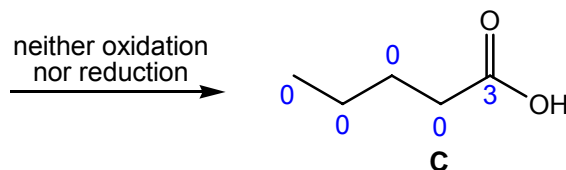
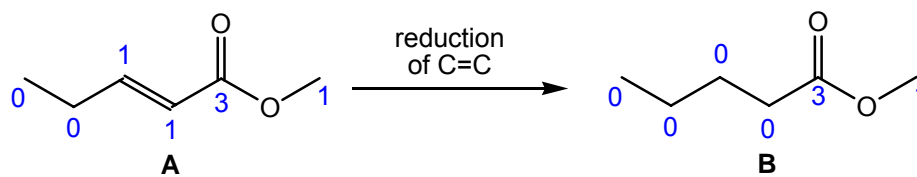
Solution

There are six carbon atoms in molecule **A**. The highest oxidation level, +3, is at the carbonyl group, and the lowest oxidation level, 0, is at the alkyl CH₃ and CH₂ groups.

For the conversion **A** → **B**, there is a decrease in the oxidation level of two carbon atoms in **A** from +1 to 0 (in **B**). Overall, this step involves a reduction at both carbon atoms of the alkene, in **A**, to give an alkane, in **B**.

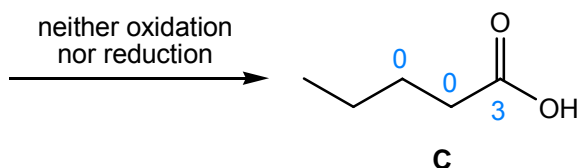
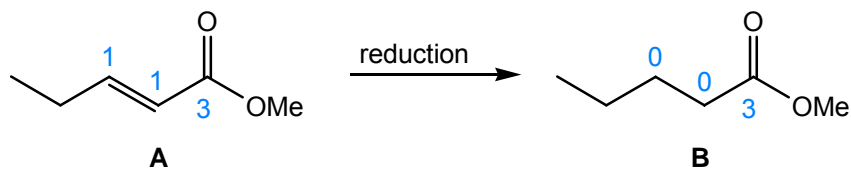
For the conversion **B** → **C**, there is no change in the oxidation levels of these molecules, so this transformation involves neither an oxidation nor a reduction.

Potential reagents for these conversions are Pd, H₂ (for **A** → **B**) and NaOH, H₂O (followed by an acidic work-up) (for **B** → **C**).



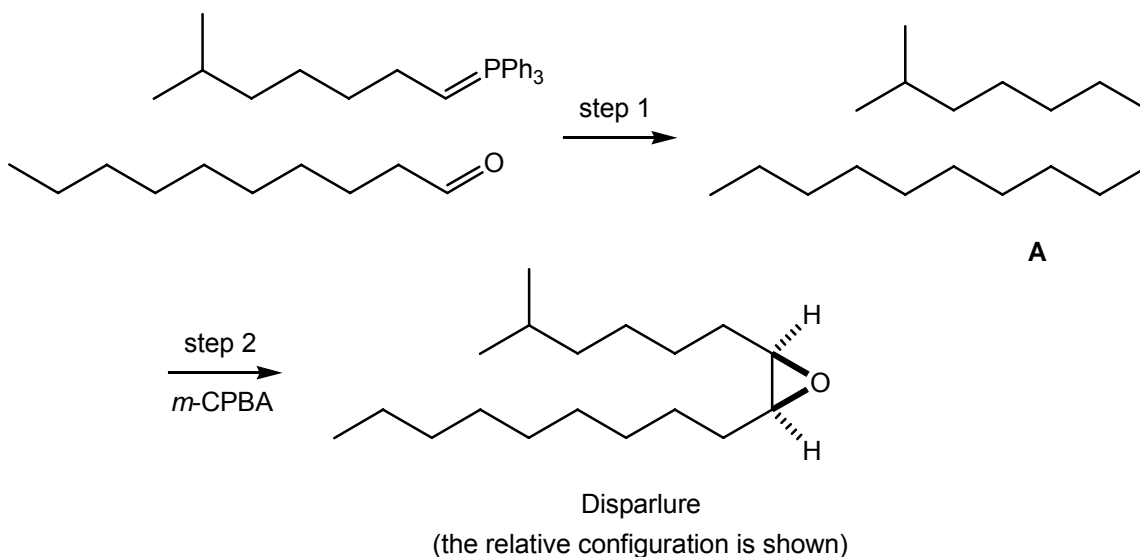
Answer

Only the important oxidation levels need to be shown.



WE 19.7 Selective reactions (on p. 908 in *Chemistry*³)

Disparlure is a natural pheromone produced by female gypsy moths to attract males for mating. A racemic synthesis is shown below.



(a) Explain why step 1 is classed as a stereoselective reaction.

Strategy

For a step to be stereoselective, it must involve the formation of stereoisomers (stereo-) and it must be selective; *i.e.*, **stereoselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Solution

Step 1 is stereoselective because it has the potential to form both the *cis*- and *trans*-alkenes. It selectively forms the major *cis*-alkene **A** [or (*Z*)-alkene]; the minor *trans*-alkene [(*E*)-alkene] is not drawn.

Answer

Step 1 is stereoselective because it leads to the selective formation of an alkene with (*Z*)- rather than (*E*)-configuration.

(b) Why is step 2 classed as a stereospecific reaction?

Strategy

For a step to be stereospecific, it must involve the formation of a single stereoisomer and there is **no choice** within its mechanism.

Solution

Step 2 is stereospecific as this oxidation can only lead to one epoxide. The major *cis*-alkene **A** leads stereospecifically to the *syn*-epoxide (as drawn). Formation of the *anti*-epoxide is mechanistically impossible!

Answer

Step 2 is stereospecific because the (*Z*)-alkene forms the *cis*-epoxide. The corresponding (*E*)-alkene would form the corresponding *trans*-epoxide.

(c) Is step 2 an enantioselective or diastereoselective reaction?

Strategy

For a reaction to be enantio- or diastereoselective it must be capable of forming a mixture of enantiomers or diastereoisomers, respectively.

Solution

In this step, both enantiomers of disparlure are formed as epoxidation of the achiral alkene **A** occurs equally on both faces to give a racemic mixture; this process is not selective as it does not select over either enantiomer. This step cannot be diastereoselective as only the *syn*-epoxide can be formed. Step 2 is neither enantioselective nor diastereoselective; it is a **diastereospecific** reaction.

Answer

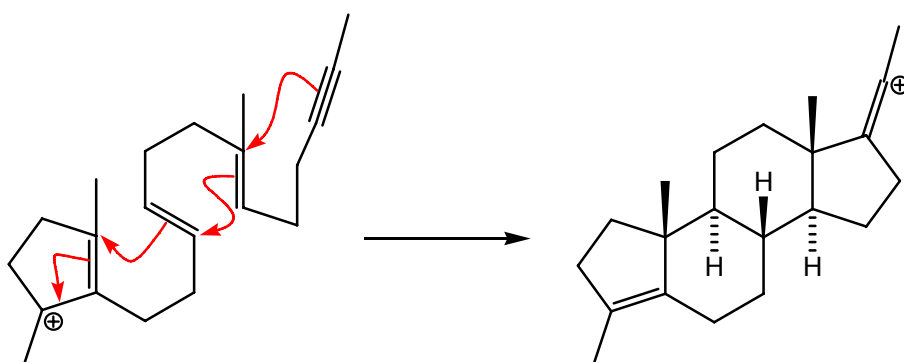
Step 2 is neither enantioselective nor diastereoselective. It is diastereospecific as only one diastereoisomer is formed. Reaction of this (*Z*)-alkene with the achiral peroxy-carboxylic acid forms a racemic mixture of one diastereoisomeric epoxide.

Answers to boxes

Box 19.2 Natural cascades (on p. 862 in *Chemistry*³)

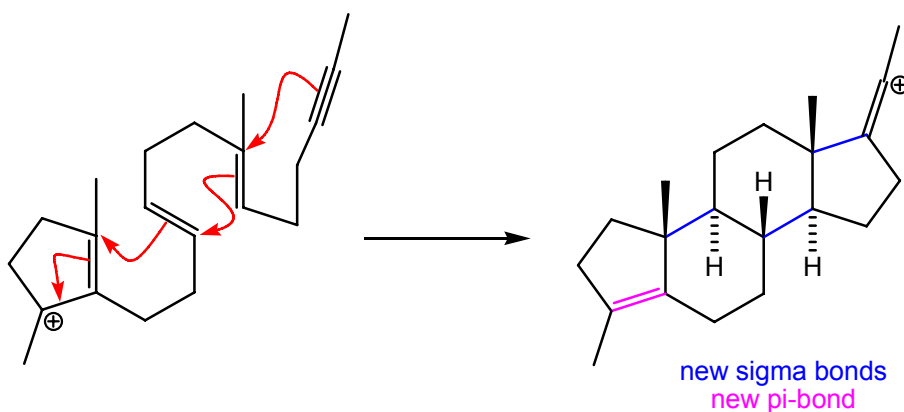
The occurrence of a cascade reaction (to form steroids) in nature has inspired researchers to mimic this type of reaction in the laboratory. This is called **biomimetic synthesis**. An example of a biomimetic cascade reaction, to form a similar ring system to that found in steroids, is shown here.

- (a) Identify the new **sigma**-bonds that are formed in the cascade reaction.



Strategy

The easiest way to find where the new **sigma**-bonds have been formed, is to overlap the carbon skeletons of the starting material and the product.

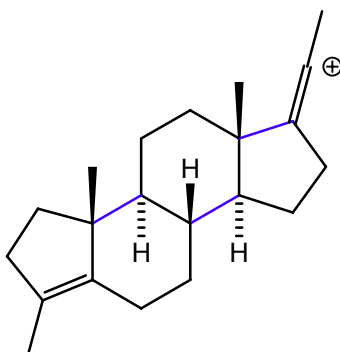


Solution

By overlapping carbon skeletons of the starting material and the product, it is obvious that there are **three new sigma bonds** and **one new pi bond** formed. The total number of new bonds formed generally equals the number of curly arrows drawn (as each arrow symbolises a pair of electrons).

Answer

(a)



three new sigma bonds

(b) Identify the chiral centres in the product, and draw its enantiomer.

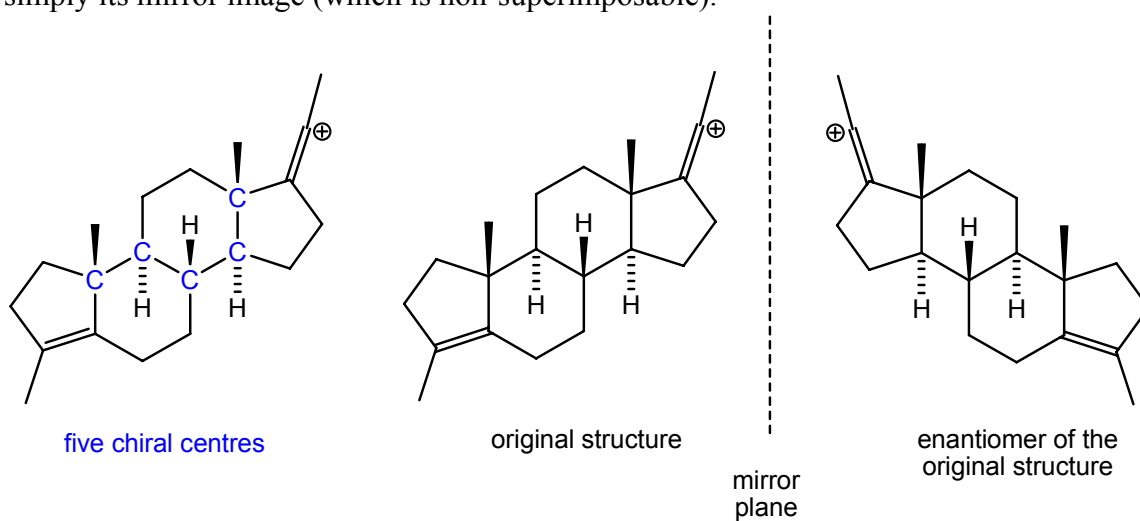
Strategy

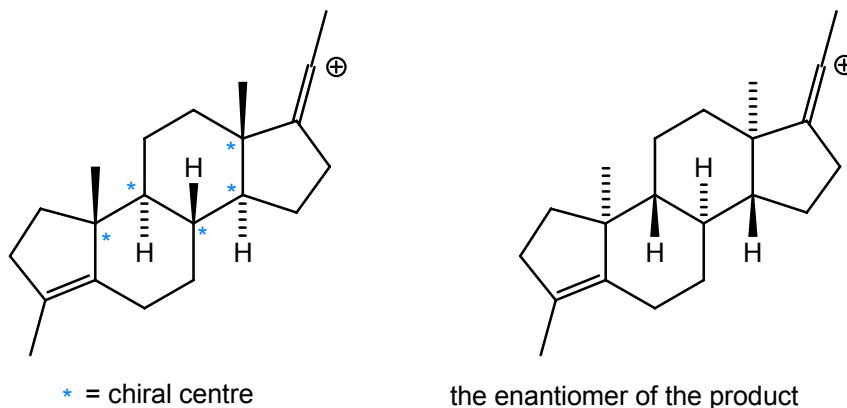
For an atom to be a chiral centre it must have four different substituents attached to it. Work out how many chiral centres there are in this molecule. It is worth while checking if there are any other elements of symmetry present (which will reduce this number).

As enantiomers are non-superimposable mirror images of each other, the enantiomer of this product will simply be its mirror image.

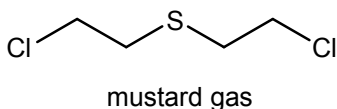
Solution

There are five chiral centres in this molecule; each is highlighted as a **blue carbon atom, C**. There are no other elements of symmetry present. The enantiomer of this product is simply its mirror image (which is non-superimposable).



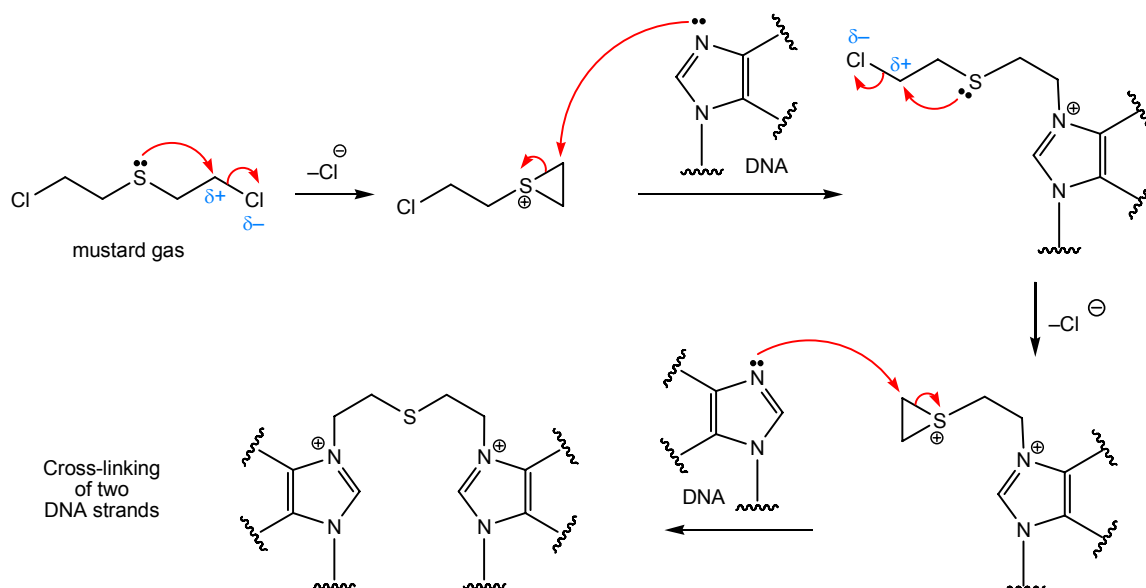
Answer**Box 19.4 Anticancer agents (on p. 882 in *Chemistry*³)**

Mustard gas is a chemical warfare agent, first used in World War 1, which stops cell division by cross-linking DNA. Propose a mechanism to show how mustard gas is able to cross-link DNA.

Strategy

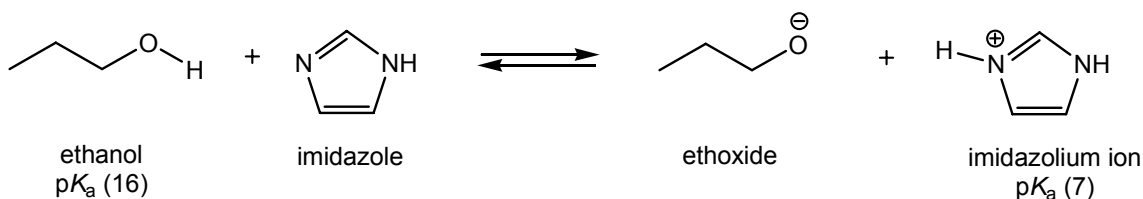
Review the mechanism given for the nitrogen mustard, mechlorethanmine, which is outlined in box 19.4 on p. 881 in *Chemistry*³. Replace the methylamino (-NMe-) group in mechlorethanmine for a sulfanyl (-S-) group, and repeat the same mechanism. Note that sulfur has TWO non-bonded pairs of electrons in which only ONE of these are used.

Solution/Answer



Box 19.6 Natural acid–base catalysis (on p. 895 in *Chemistry*³)

In step 1, in the above mechanism, chymotrypsin produces an alkoxide ion by deprotonation of an alcohol using an imidazole group as the base. In the absence of the enzyme, where would you expect the equilibrium of the reaction of ethanol with imidazole to lie?



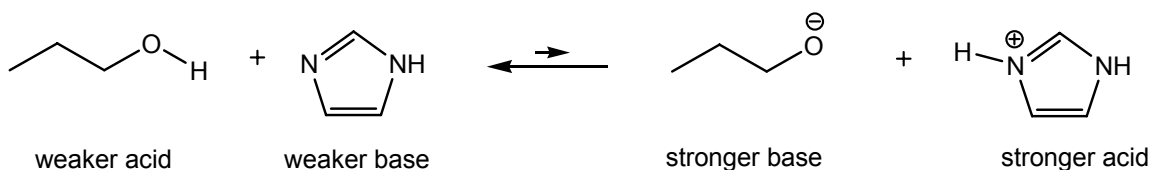
Strategy

Examine the pK_a values for both acids. The equilibrium will favour the more stable (and less acidic) acid.

Solution

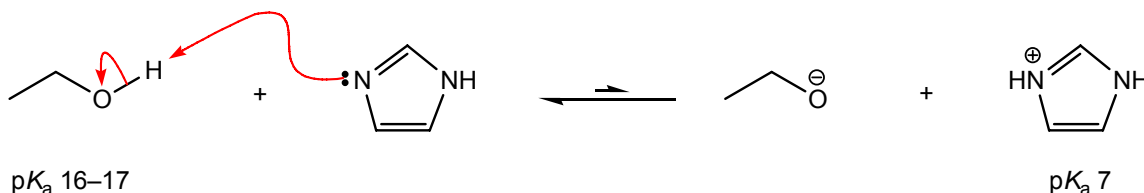
Ethanol (pK_a 16) is less acidic than the imidazolium ion (pK_a 7), and therefore the equilibrium will favour the left-hand side of this equilibrium (the ethanol side). Also,

ethoxide is more basic than imidazole, so the overall equilibrium favours the left-hand side as shown below:



Answer

The conjugate acid of imidazole has a lower pK_a than ethanol, and therefore has a greater tendency to donate a proton. The equilibrium will lie to the left-hand side.



Box 19.8 Superglue and fingerprints (on p. 902 in *Chemistry*³)

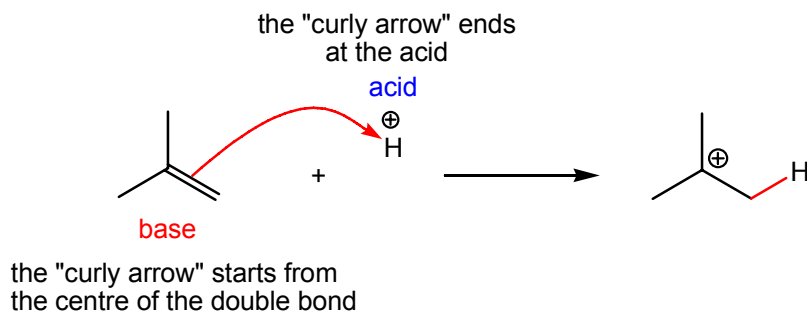
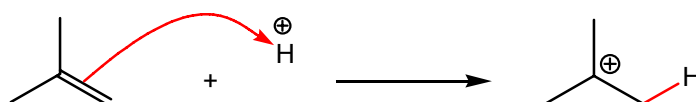
The polymerization of ethyl 2-cyanoacrylate by hydroxide ion is an example of an **anionic polymerization**. Alkenes also undergo polymerization by reaction mechanisms that involve radicals or carbocations. For example, the **cationic polymerization** of 2-methylpropene (isobutylene) can be promoted by the addition of a small amount of an acid as shown on p. 902 in *Chemistry*³.

(a) Use a curly arrow to show the mechanism of step 1.

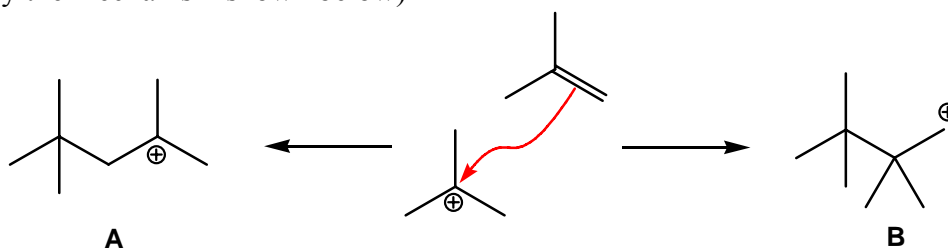
Strategy

H^+ contains no electrons, and therefore the curly arrow must start at the centre of the pi-bond of this alkene, where the two pi-electrons reside. As this alkene is unsymmetrical alkene, protonation can lead to two carbocations. Only the more stable and preferred tertiary carbocation is drawn in this question.

Solution

Answer

- (b) Explain why carbocation **A** is formed in step 2, rather than carbocation **B** (formed by the mechanism shown below)

Strategy

Examine the structure of both carbocations, **A** and **B**. The **more** stable carbocation is generally the **more** preferred.

Solution

Carbocation **A** is the more stable and more substituted tertiary carbocation. This carbocation can be stabilised through hyperconjugation using its adjacent alkyl substituents. Carbocation **B** is the less stable and less substituted primary carbocation. This carbocation cannot be stabilised by hyperconjugation as there are **no** adjacent primary, secondary or tertiary alkyl substituents, which are capable of donating their alpha C-H bonds. For additional information about hyperconjugation, see p. 870 in *Chemistry*³.

Answer

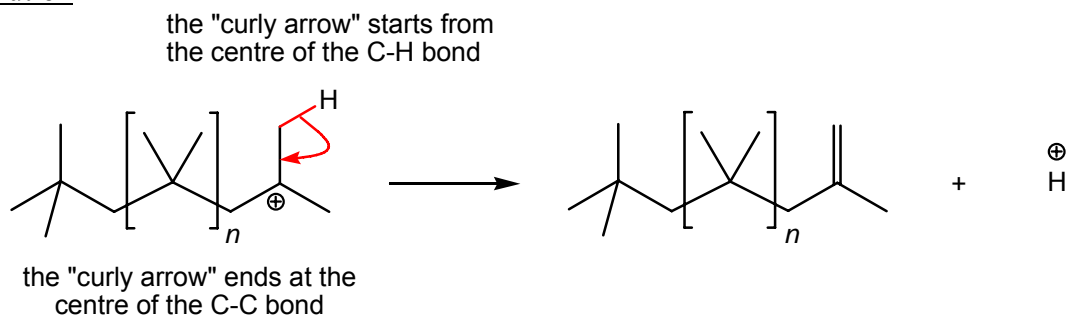
The reaction forms tertiary carbocation **A**, rather than primary carbocation **B**, because tertiary carbocation **A** is the more stable carbocation. The tertiary carbocation **A** has three +I groups that delocalise the charge, whereas this primary carbocation **B** has **no** +I groups which can delocalise the charge.

(c) Use a curly arrow to show the mechanism of step 3.

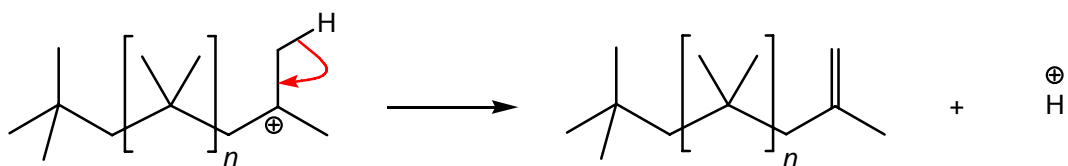
Strategy

This step involves deprotonation. The byproduct of this reaction is H^+ which comes from the heterolytic cleavage of the C-H bond. Draw a curly arrow from the centre of this C-H bond, and as the other product is an alkene, make sure the double headed arrow ends in the middle of where the alkene is formed.

Solution



Answer



Answers to end of chapter questions (on p. 911 in *Chemistry*³)

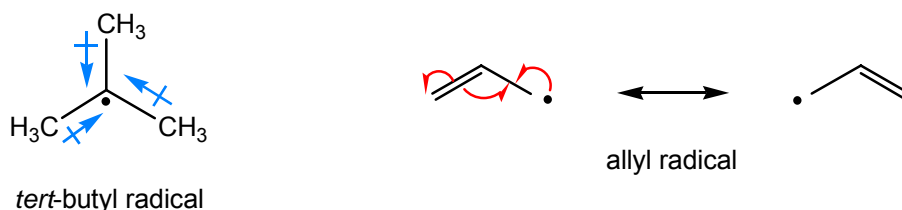
1. Use the symbols +I, -I, +M, -M to identify the inductive and mesomeric effects of the following groups: (a) -Et; (b) -CHO; (c) -NO₂; (d) -NH₂; (e) -OCH₃; (f) -CO₂CH₃.

Strategy

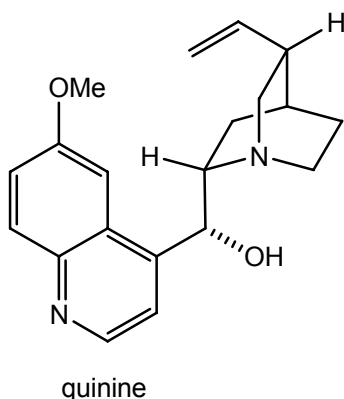
Draw out each substituent, determine the hybridisation of its principal atom and include any non-bonded pairs of electrons. Inductive (I) and mesomeric (M) effects involve sigma and pi-frameworks respectively; a +VE sign means the substituent is electron-donating, and a -VE sign means its electron-withdrawing. Interestingly, there is no mesomeric effect for a principal atom which is sp^3 -hybridised. If this principal atom is sp^2 -hybridised, and contains a non-bonded pair of electrons then it has a +M effect, and if it does not, it has a -M effect. If the principal atom has an electronegative atom attached to it, it will have a -I effect, or hydrogen atoms, it will have a +I effect.

Solution

- (a) -Et group; its principal atom is a sp^3 -hybridised carbon atom; therefore, it has no mesomeric effect. This group has a +I effect as it can donate electron-density through hyperconjugation.
- (b) -CHO group; its principal atom is a sp^2 -hybridised carbon atom. As there is no non-bonded pair of electrons on this atom, it will have a -M effect. It also has a -I effect due to the electronegative β -oxygen atom.
- (c) -NO₂ group; its principal atom is a sp^2 -hybridised nitrogen atom. As there is no non-bonded pair of electrons on this atom, it will have a -M effect. It also has a -I effect due to this electronegative nitrogen atom.
- (d) -NH₂ group; its principal atom is a sp^2 -hybridised nitrogen atom. As there is a non-bonded pair of electrons on this atom, it will have a +M effect. It also has a -I effect due to this electronegative nitrogen atom.
- (e) -OMe group; its principal atom is a sp^2 -hybridised oxygen atom. As there is (at least) one non-bonded pair of electrons on this atom, it will have a +M effect. It also has a -I effect due to this electronegative oxygen atom.
- (f) -CO₂Me group; its principal atom is a sp^2 -hybridised carbon atom. As there is no non-bonded pair of electrons on this atom, it will have a -M effect. It also has a -I effect due to the two electronegative β -oxygen atoms.



5. The following questions relate to quinine, a naturally occurring antimalarial agent.



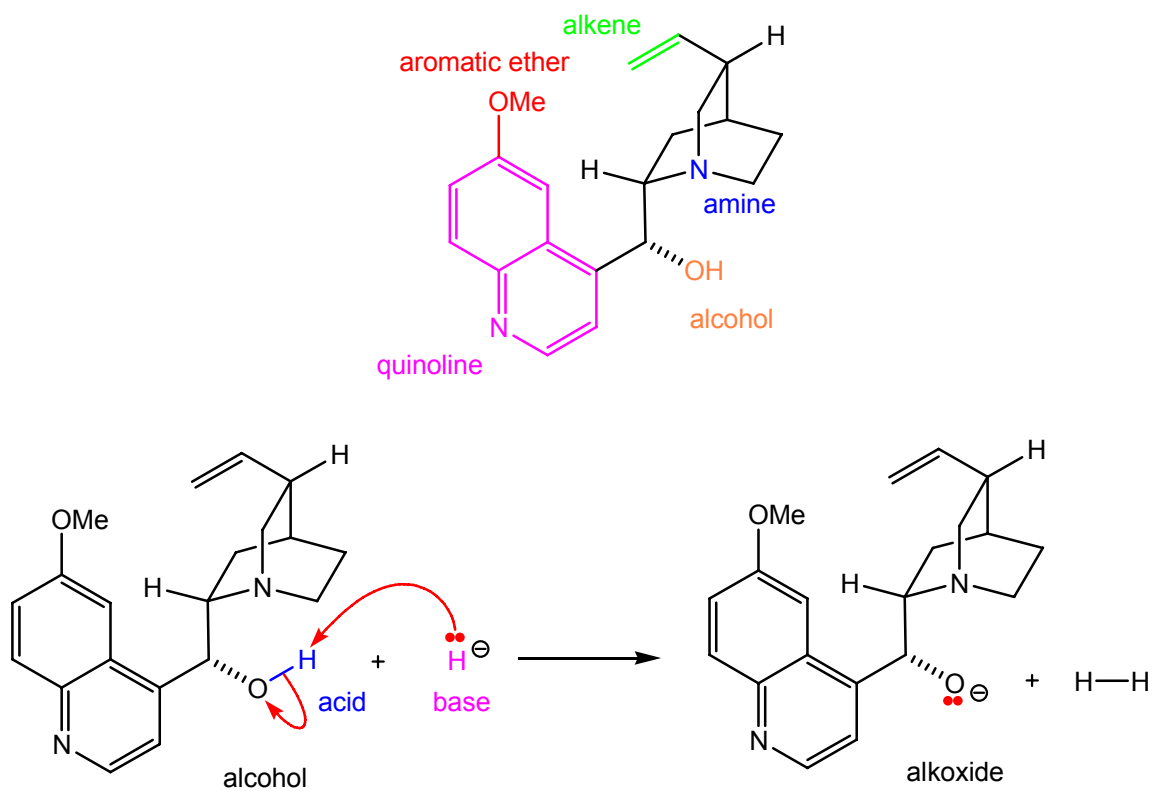
- (a) (i) Identify, giving your reasons, the most acidic hydrogen atom in quinine.
 (ii) Draw the product from the reaction of quinine with sodium hydride (Na^+H^-) and give a mechanism (using curly arrows) to show its formation.

Strategy

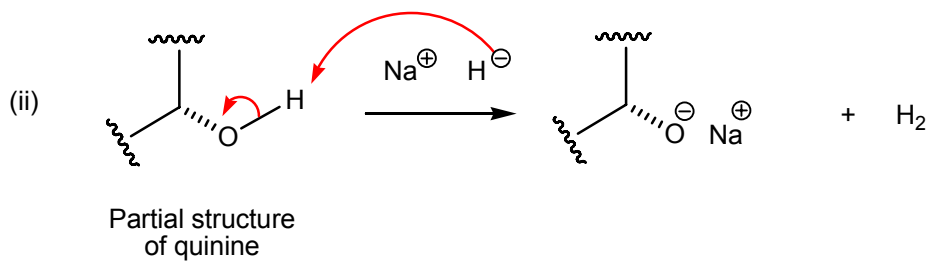
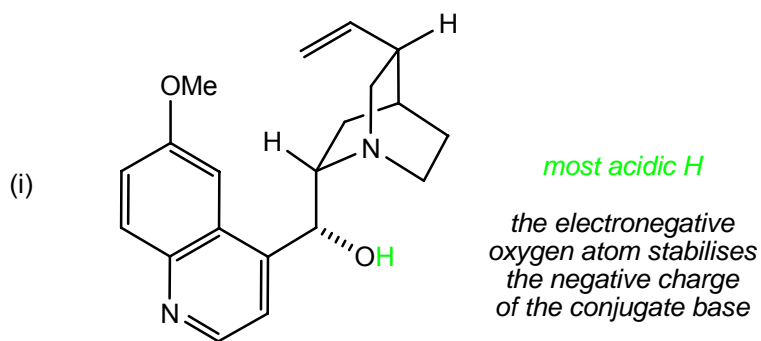
Name all the functional groups present in this molecule (this might give you a clue to which proton is the most acidic). Using hydride, H^- , as the Brønsted base, remove the most acidic proton from this molecule. For this mechanism, you will need two “curly arrows”; one from the hydride to the proton of your chosen Brønsted acid (\rightarrow), and one from the centre of this C-H bond to the principal atom of this acid (\rightarrow).

Solution

There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The alcohol group contains the most acidic proton ($\text{p}K_{\text{a}} = 16$) as its conjugate base, alkoxide, is stabilised by its highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below. [Note: hydride, H^- , contains a pair of non-bonded electrons.]



Answer



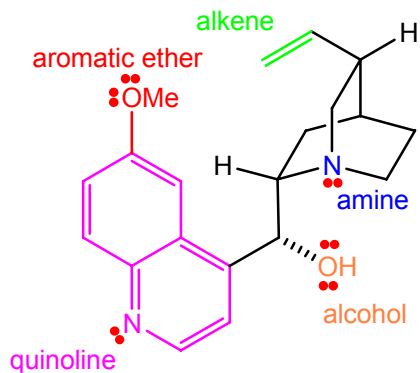
- (b) (i) Identify, giving your reasons, the most basic functional group in quinine.
 (ii) Draw the product from the reaction of quinine with hydrogen chloride (H-Cl) and give a mechanism (using curly arrows) to show its formation.

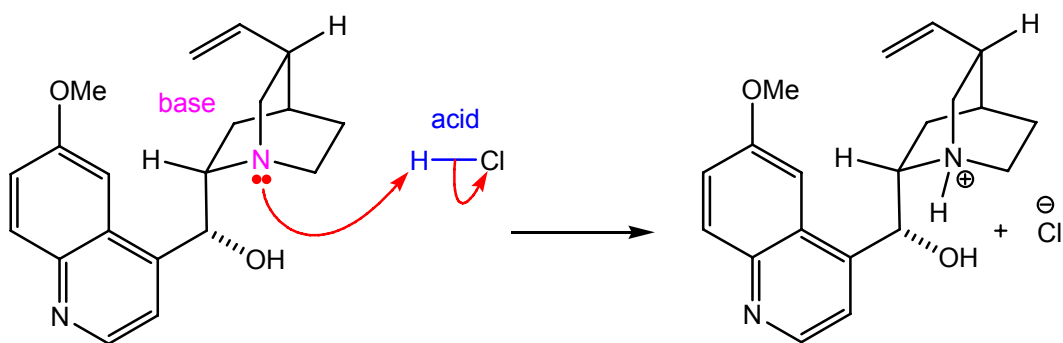
Strategy

Name all the functional groups present in this molecule and include all non-bonded pairs of electrons (this might give you a clue to which principal atom is the most basic). Using hydrogen chloride, H-Cl, as the Brønsted acid, remove this proton using the principal atom of your chosen Brønsted base. For this mechanism, you will need two “curly arrows”; one from the principal atom of your chosen Brønsted base to the proton of H-Cl (\rightarrow), and one from the centre of this H-Cl bond to the principal atom of this acid, Cl (\rightarrow).

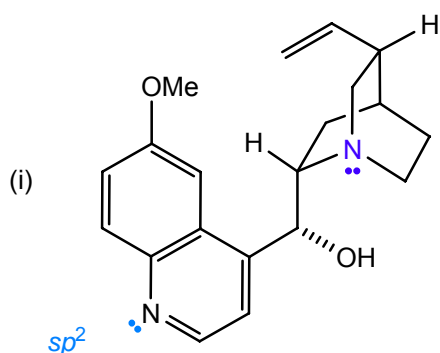
Solution

There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The tertiary amine group is the most basic group as it contains the more basic nitrogen atom; sp^3 -hybridised amines are more basic than sp^2 -hybridised quinolines as their non-bonded pair of electrons is higher in energy. The alcohol and ether are less basic as their principal atom is a highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below.





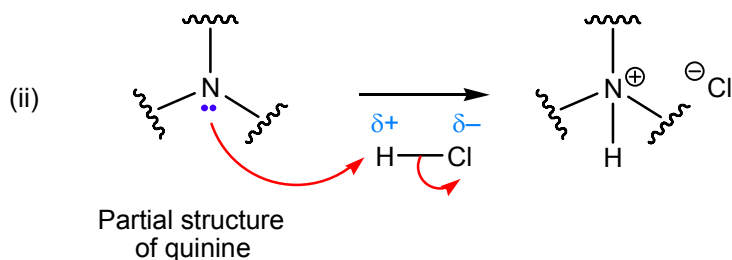
Answer



most basic site

amines are more basic than alcohols or ethers because nitrogen is less electronegative than oxygen

the lone pair on this nitrogen atom is in an sp^3 orbital and this is more basic than a lone pair in an sp^2 orbital



- (c) (i) Identify, giving your reasons, the most nucleophilic site in quinine.
 (ii) Draw the product from the reaction of quinine with CH_3Br and give a mechanism (using curly arrows) to show its formation.

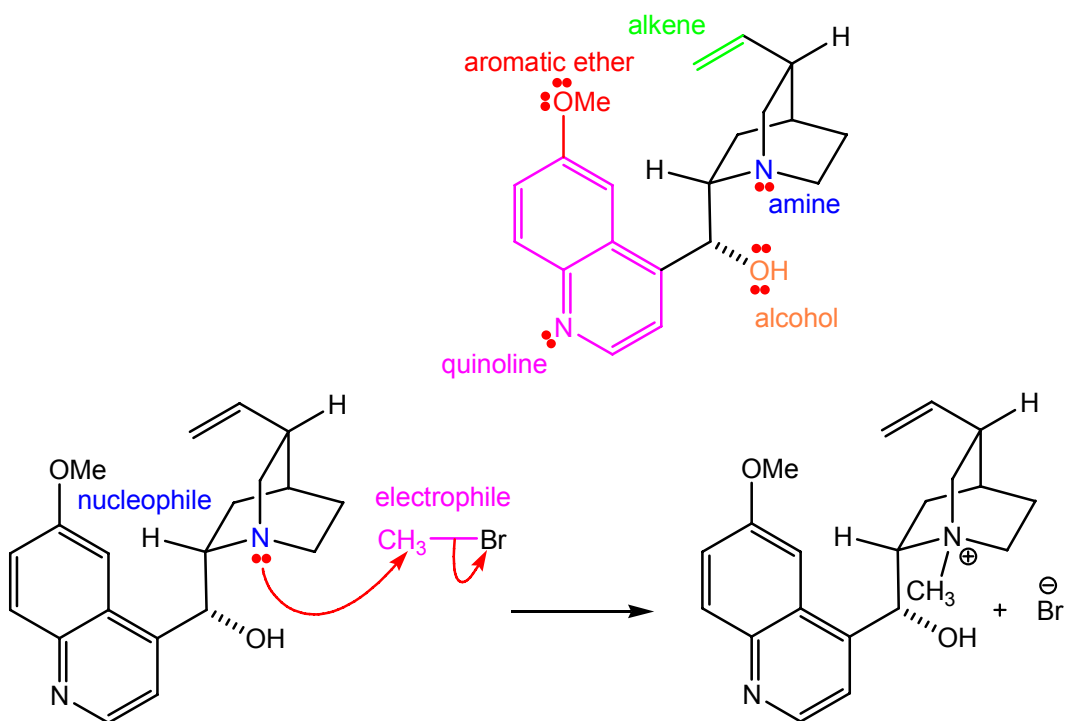
Strategy

Name all the functional groups present in this molecule and include all non-bonded pairs of electrons (this might give you a clue to which principal atom is the most nucleophilic). Using methyl bromide, $\text{CH}_3\text{-Br}$, as the electrophile; transfer this methyl (CH_3) group using the principal atom of your chosen nucleophile. For this mechanism, you will need

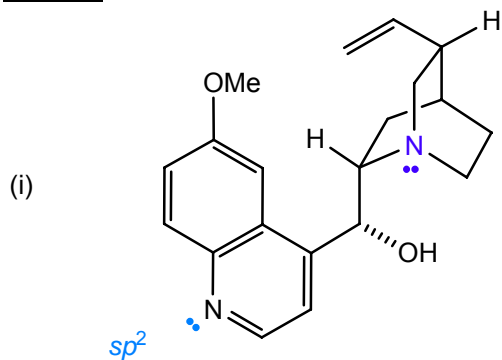
two “curly arrows”; one from the principal atom of your chosen nucleophile to the methyl group of $\text{CH}_3\text{-Br}$ (\rightarrow), and one from the centre of this $\text{CH}_3\text{-Br}$ bond to the principal atom of this electrophile, bromide (\rightarrow).

Solution

There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The tertiary amine group is the most nucleophilic group as it contains the more nucleophilic nitrogen atom; sp^3 -hybridised amines are more nucleophilic than sp^2 -hybridised quinolines as their non-bonded pair of electrons is higher in energy. The alcohol and ether are less nucleophilic as their principal atom is a highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below.



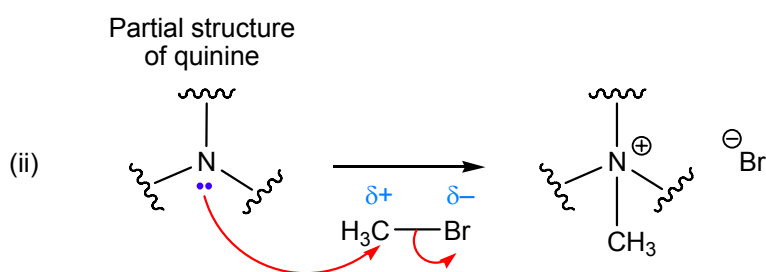
Answer



most nucleophilic site

amines are more nucleophilic than alcohols or ethers because nitrogen is less electronegative than oxygen.

the lone pair on this nitrogen atom is in an sp^3 orbital and this is more nucleophilic than a lone pair in an sp^2 orbital



Solutions provided by J. Eames (j.eames@hull.ac.uk)